REMARKS

Exemplary support for the revision to part (c) of claim 3 can be found in the Specification at page 9, lines 7-11 and page 25, lines 14-16.

Comments regarding restriction requirement and claim objections

Claims 14, 15, 16, 28 and 29 are "method of use" claims which all depend from the independent product claims 3 and 12. Therefore, upon allowance of product claims 3 and 12, the method of use claims 14, 15, 16, 28 and 29 should be rejoined and considered together, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

It is believed that the above amendments also address the Examiner's concerns regarding claim dependency. Withdrawal of the objections concerning such matters is therefore believed to be in order.

Objection to the Specification

The Specification has been objected to as it has been alleged that the description on page 34, line 19, does not relate to conditions or diseases that can be diagnosed with HCOR. Such, however, is not the case. It is respectfully submitted that the this portion of the Specification has not been read in its correct context. That is, the relevant passage at lines 18-20 describes "inflammatory responses necessary to kill microorganisms, removed damaged tissues, and prepare the region for tissue repair or regeneration." Thus, "removed damaged tissues, and prepare the region for tissue repair or regeneration" are associated with "inflammatory responses" and, therefore, are properly considered conditions for diagnosis.

Utility rejection under 35 U.S.C. § 101 and § 112, first paragraph

Claims 3-7, 9, 10, 12 and 13 stand rejected under 35 U.S.C. § 101 and § 112, first paragraph based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that:

- "...the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility". (Office Action, November 19, 2003; page 4).
- "...since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention". (Office Action, November 19, 2003, page 6).

The rejection of Claims 3-7, 9, 10, 12 and 13 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a C5a-like receptor that is expressed in thymus tissue in humans. The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Applicants submit with this paper two expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before or shortly after the November 23, 1998 priority date of the instant application. The Rockett Declaration and the Iyer Declaration, and the ten (10) references establish that, prior to the filing dates of the provisional applications to which the subject application is benefitted priority, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies

conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise

knowledge of its biological function, or the biological function of the polypeptide it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Rockett Declaration and the Iyer Declaration the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

The claims have also been rejected for lack of utility under 35 U.S.C. §112, first paragraph. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Enablement rejection of claim 7 under 35 U.S.C. § 112, first paragraph

The Office Action (page 6) has also set forth a rejection of claim 7 under 35 U.S.C. §112, first paragraph, based on the theory that the claimed transformed cell could be used in a human as a part of gene therapy, and such use is not enabled. This position is improper as it reads process limitations into the claim. That is, claim 7 is directed to a tranformed cell, not a method of using a transformed cell in gene therapy. There are many uses of the claimed transformed cell besides gene therapy, such as its use in recombinant methods to make a polypeptide comprising the amino acid sequence of SEQ ID NO:1. Hence, a rejection for lack of enablement of the claimed transformed cell is improper, and should be withdrawn.

Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 3, 6, 7, 9, 12 and 13 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had in possession of the claimed invention. Applicants traverse the rejection, as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46] (Footnotes are omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The subject matter encompassed by claims 3, 6, 7, 9, 12 and 13 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 3 recites a "polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1". Similar wording is found in independent claim 12, which recites " a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2." The amino acid sequence of SEQ ID NO:1 and the polynucleotide sequence of SEQ ID NO:2 are explicitly disclosed in the Specification as filed (see, for example, the Sequence Listing). Variants are described in the Specification at, for example, page 11, line 29 to page 12, line 2. Given any naturally occurring amino acid or polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1 or SEQ ID NO:2. Accordingly, the specification provides an adequate written description of the recited polypeptide variants of SEQ ID NO:1 and polynucleotide variants of SEQ ID NO:2.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate

written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides and

polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claims 3 and 12 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
>
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
>
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, and
>
> c) an immunogenic fragment of at least 10 contiguous amino acids of a polypeptide having the amino acid sequence of SEQ ID NO:1.
>
> 12. An isolated polynucleotide selected from the group consisting of:
>
> a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,
>
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,
>
> c) a polynucleotide complementary to a polynucleotide of a),
>
> d) a polynucleotide complementary to a polynucleotide of b), and
>
> e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its

written description inquiry "on whatever is now claimed," the Office Action fails to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as C5a-like receptor proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "90% variants" recited by the present claims have a variation that is far less than that of all potential C5a-like receptor proteins related to SEQ ID NO:1, i.e., those C5a-like receptor proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1. Therefore, the skilled artisan would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a C5a-like receptor protein.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of January 31, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have

stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides and polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

Indefiniteness rejection under 35 U.S.C. §112, second paragraph

Claims 3, 6, 7, 9 and 10 were rejected under the second paragraph of 35 U.S.C. §112 for alleged indefiniteness. This rejection is traversed.

The Office Action asserted that the phrase "biologically active" is indefinite. While not conceding as to the propriety of this rejection, that phrase has been deleted from the claims in order to expedite prosecution of the subject application.

In addition, the Office Action alleged that the phrase "naturally occurring" is indefinite. Such, however, is not the case. In pertinent part, claim 3 recites "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, and claim 12 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2." Hence, "naturally occurring" merely refers to the source of the amino acid or polynucleotide sequence, *i.e.*, the sequence must be found in nature. However, the polypeptide or polynucleotide recited by the claim can be made by any means, such as isolation from nature or manufacture by chemical or recombinant methods. It is the amino acid or polynucleotide *sequence* which must be found in nature.

For at least the above reasons, the meaning of the claims is clear. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is therefore requested.

Rejections under 35 U.S.C. §102

Claims 3, 6, 7 and 9 were rejected under 35 U.S.C. §102(b) as being anticipated by Gerard et al (Nature, 349:614, 1991). According to the Office Action, Gerard et al is pertinent to certain polynucleotides recited by the claims because Gerard et al allegedly describes a polynucleotide sequence which encodes a polypeptide that includes the amino acid sequence VFLVG. While not conceding as to the propriety of this position, the claims have been revised to recite, *inter alia*, a polynucleotide which encodes an immunogenic fragment of at least 10 contiguous amino acids of a polypeptide having the amino acid sequence of SEQ ID NO:1. Gerard et al does not disclose or suggest such a molecule.

Claims 3, 4, 6, 7, 9, 10, 12 and were rejected under 35 U.S.C. §102(b) as being anticipated by Jacobs et al (U.S. Patent No. 5,723,315). In addition, claims 3, 6, 7, 9, 12 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Ruben et al (WO 98/54206). Both of these rejections are based on the theory that Applicants are not due the benefit of their parent application Serial No. 08/791,974 because the claimed subject matter allegedly fails to meet the requirements of 35 U.S.C. §112, first paragraph, due lack of utility. As explained above, the claimed subject matter meets the statutory utility requirement. Thus, the present application is due the benefit of the parent filing date of January 31, 1997, and neither Jacobs et al. nor Ruben et al is prior art to the subject application.

For at least the above reasons, withdrawal of the §102 rejections is believed to be in order.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: 19 February 2004

Richard C. Ekstrom

Reg. No. 37,027

Direct Dial Telephone: (650) 843-7352

Customer No.: 27904

3160 Porter Drive

Palo Alto, California 94304

Phone: (650) 855-0555

Fax: (650) 849-8886